JACC: CARDIOVASCULAR IMAGING VOL. 6, NO. 6, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2012.09.020

Myocardial Extracellular Volume Fraction From T1 Measurements in Healthy Volunteers and Mice

Relationship to Aging and Cardiac Dimensions

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OBJECTIVES This study aimed to test the characteristics of the myocardial extracellular volume fraction (ECV) derived from pre- and post-contrast T1 measurements among healthy volunteers.

BACKGROUND Cardiac magnetic resonance (CMR) T1 measurements of myocardium and blood before and after contrast allow quantification of the ECV, a tissue parameter that has been shown to change in proportion to the connective tissue fraction.

METHODS Healthy volunteers underwent standard CMR imaging with administration of gadolinium. T1 measurements were performed with a Look-Locker sequence followed by gradient-echo acquisition. We tested the segmental, interslice, inter-, intra-, and test-retest characteristics of the ECV, as well as the association of the ECV with other variables. Juvenile and aged mice underwent a similar protocol, and cardiac sections were harvested for measurement of fibrosis.

RESULTS In healthy volunteers (N = 32, 56% female; age 21 to 72 years), the ECV averaged 0.28 ± 0.03 (range 0.23 to 0.33). The intraclass coefficients for the intraobserver, interobserver, and test-retest absolute agreements of the ECV were 0.94 (95% confidence interval: 0.84 to 0.98), 0.93 (95% confidence interval: 0.80 to 0.98), and 0.95 (95% confidence interval: 0.52 to 0.99), respectively. In volunteers, the ECV was associated with age ($r = 0.74$, $p < 0.001$), maximal left atrial volume index ($r = 0.67$, $p < 0.001$), and indexed left ventricular mass. There were no differences in the ECV between segments in a slice or between slices. In mice (N = 12), the myocardial ECV ranged from 0.20 to 0.32 and increased with age (0.22 ± 0.02 vs. 0.30 ± 0.02, juvenile vs. aged mice, $p < 0.001$). In mice, the ECV correlated with the extent of myocardial fibrosis ($r = 0.94$, $p < 0.001$).

CONCLUSIONS In healthy volunteers, the myocardial ECV ranges from 0.23 to 0.33, has acceptable test characteristics, and is associated with age, left atrial volume, and left ventricular mass. In mice, the ECV also increases with age and strongly correlates with the extent of myocardial fibrosis. (J Am Coll Cardiol Img 2013;6:672–83) © 2013 by the American College of Cardiology Foundation

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The presence of focal myocardial fibrosis is associated with adverse cardiovascular outcomes (1 3). Various imaging techniques have emerged to quantify myocardial fibrosis noninvasively. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) is the current optimal noninvasive technique for detection and quantification of myocardial scar and replacement fibrosis (4). However, limitations exist to LGE-based techniques for the detection of diffuse or interstitial myocardial fibrosis. Comparison with pathological standards reveals a marked consistent

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underestimation of both the presence and extent of diffuse fibrosis (5 7). The LGE technique relies on relative enhancement of an abnormal region of myocardium compared with a normal reference. In conditions such as hypertension, sleep apnea, valvular disease, diabetes, obesity, and nonischemic cardiomyopathy, the entire left ventricle may be affected by adverse tissue remodeling, and a normal myocardial reference region may be inappropriately identified. Furthermore, the optimal threshold for quantifying LGE in the presence of diffuse or patchy fibrosis is not well defined (8). These limitations have prompted research into novel CMR-based quantitative techniques for measurement of the myocardial extracellular volume fraction (ECV).

The myocardial ECV increases in proportion to the connective tissue fraction and can be regarded as a continuous measurement of the extent of accumulation of myocardial fibrosis (9 11). T1 mapping is a novel CMR-based technique in which measured differences in R1 (= 1/T1) values before and after gadolinium allow quantification of myocardial ECV (9,12 15). The CMR T1 technique has the potential to differentiate myocardial fibrosis on a continuous scale, from normal myocardium, through diffuse myocardial fibrosis, and ultimately to myocardial scar (16,17). However, limited data exist on the myocardial ECV in a normal healthy population, on the test characteristics of this evolving technique, the optimal CMR protocol for measurement of the myocardial ECV, and on the associations between the ECV and other clinical and imaging variables. Thus, our aims were 2-fold. We first wanted to define a normal reference range in a healthy population, as well as define the test characteristics of the myocardial ECV measurement. The second aim was to test our hypothesis that the myocardial ECV measurement is associated with histological evidence of myocardial fibrosis.

METHODS

Study protocol. The protocol was approved by the Partners Healthcare System Human Subjects Review Committee in the Brigham and Women's Hospital. We recruited healthy volunteer controls by open enrollment. We specifically excluded volunteers with chest pain on exertion; any active or prior history of heart disease, stroke, diabetes, malignancy, sleep apnea, hypertension, an irregular heart rhythm or atrial fibrillation; or any form of kidney disease. Screening consisted of a comprehensive questionnaire detailing medical and medication history, standard anthropometric data, and measurement of blood pressure, pulse, serum creatinine, and hematocrit.

To determine whether aging was associated with a change in the myocardial ECV in mice and to assess whether aging was associated with a change in the extent of myocardial fibrosis, we performed the following protocol in juvenile and aged mice. Juvenile C57BL/6 aged 4 weeks (n = 4) and aged C57BL/6 aged 48 weeks (n = 8) underwent a CMR study. After the CMR study, mice were euthanized, and cardiac sections were analyzed for the presence of myocardial fibrosis using Masson's trichrome. Serum hematocrit was recorded on the day mice were killed immediately after the CMR study. The protocol was approved by the Institutional Animal Care and Use Committee at Harvard University.

Human CMR protocol. All images were acquired with electrocardiographic gating, breath-holding, and the patient in a supine position. Patients were imaged on 3.0-T CMR system (Tim Trio, Siemens, Erlangen, Germany). The basic CMR

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CMR = cardiac magnetic resonance

ECV = extracellular volume fraction

LGE = late gadolinium enhancement

LV = left ventricular

MOLLI = modified Lock-Locker inversion recovery

ShMOLLI = shortened modified Lock-Locker inversion recovery

previously by an NIH T32 Training Grant (T32HL09430101A1). Dr. Mongeon receives financial support for research from the Montreal Heart Institute Foundation, Montreal, Canada. Dr. Kwong receives salary support from a research grant from the National Institutes of Health (R01HL091157). Dr. Jerosch Herold is supported in part by a research grant from the National Institutes of Health (R01HL090634 01A1); and is listed as co inventor on a pending patent application related to detection of diffuse fibrosis by MRI. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Neilan and Coelho Filho contributed equally to this work.

Manuscript received June 11, 2012; revised manuscript received September 24, 2012, accepted September 26, 2012.